# Evaluation of Renal Vascular Disease

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## Introduction

Renal artery stenosis is a progressive disease, more than half of all high-grade stenoses progress to occlusion within only 2 years [1, 2]. A recent publication in the New England Journal of Medicine has stressed the fact that renal artery stenosis with the consequences of stenosis-induced hypertension and chronic renal failure represents only a small entity among a number of overlapping disease complexes including atherosclerotic vascular disease, primary hypertension and renal parenchymal disease [3]. In a large number of patients, chronic renal failure may occur unrelated to the presence of a diagnosed renal artery stenosis, but may be the result of much more common diseases such as essential hypertension or renal parenchymal disease from hypertensive nephrosclerosis, diabetes or glomerulonephritis [4, 5].

This may be one of the primary reasons for the sobering results from meta-analyses of interventional trials reporting only an improvement rate of about 1/3 in regard to hypertension or renal function after renal artery stenosis dilatation [6-8]. A cure of the blood pressure occurs only in about 19 % of the cases, an improvement of blood pressure in about 52 % of the cases. Restenosis after angioplasty is found in up to 30 % of the cases. The DRASTIC study in which a medical anti-hypertensive therapy was compared to PTA showed only marginal advantages for PTA [9]. In spite of some methodological weaknesses, the authors, however, found a significant reduction of medications in the interventional treatment arm and a somewhat higher rate of improvement of blood pressure in 68% vs. 38 % of the cases and even a 7 % cure rate versus no cure of blood pressure at all in the conservative medical treatment arm. Four renal artery occlusions were found in the conservative arm.

Therefore, the crucial goal in the work-up of renal artery stenosis is to identify patients, who truly reveal a hemodynamically significant renal artery stenosis and who can be expected to benefit from an interventional revascularisation. This leads to a series of diagnostic challenges for the morphologic and functional assessment of renal artery stenosis. Among all different modalities, magnetic resonance imaging (MRI) inherits the appealing advantage that it is non-invasive and does not expose the patient to potentially nephrotoxic contrast agents or ionizing radiation.

## 1. Accuracy of stenosis grading

Ideally, a 50% diameter stenosis has been defined as hemodynamically significant which corresponds to a 75% area stenosis [10]. However, it is well known from pathology studies that atherosclerosis of the vascular wall does not spread uniformly but frequently causes eccentric and irregular narrowing of the vessel lumen [11]. This has been overlooked for a long time, and for decades measurement of the diameter stenosis on digital subtraction angiography (DSA) has been and still is considered the gold standard of stenosis grading. Intravascular ultrasound (IVUS) in fact was the first modality to be used for the assessment of area stenosis in coronary angiography [12]. While this probably can be considered the true gold standard for accurate stenosis grading, its costs and its invasiveness do not make it a routine method for primary grading of renal artery stenosis.

3D Gadolinium-enhanced MR angiography (3D-Gd-MRA) initially started out as a technique to replace the invasive grading of the diameter stenosis by DSA. While the initial results of small studies from 1995 to 1999 revealed highly promising results for 3D-Gd-MRA with sensitivities and specificities exceeding 90 %, a recent Dutch multi-center trial called the RADISH (renal artery diagnostic imaging study in hypertension) presented highly discouraging results with overall sensitivities below 70 % and specificities below 90% [13]. A large percentage of these sobering results can be attributed to the lack of spatial resolution of 3D-Gd-MRA at that time with typical voxel sizes of 3 – 6 $mm^3$. This resolution makes exact numerical grading of the renal artery stenosis difficult and in a number of studies only a ordinal grading scale of three or five grades (no stenosis, stenosis less than 50 %, stenosis exceeding 50 %, stenosis exceeding 75 %, artery occluded) were applied [14]. However, with new state-of-the-art MRI techniques such as parallel imaging, high resolution data sets of the renal artery with voxel sizes of only 0.7 $mm^3$ can now be acquired within a single breathhold of 23 seconds [15]. While this by itself has improved the visualization of the renal artery stenosis, the more important effect is that now the isotropic data sets can be deliberately reformatted in any imaging plane, allowing to assess the vessel area at the site of the stenosis perpendicular to the course of the renal artery. As a consequence, even an eccentric area stenosis can be measured with satisfactory precision. This has been found to significantly improve the grading of renal artery stenosis compared to the traditional assessment of the lumen diameter. A recent publication has shown a good agreement to intravascular ultrasound [16].

## 2. Determination of hemodynamic significance of renal artery stenosis

In principle, spins moving along a magnetic field gradient are subject to phase shift, which directly corresponds to their velocity. Flow measurements in MRI require the acquisition of a flow-sensitive and a flow-compensated image, the velocity information is obtained by subtracting the two phase images. If ECG-gating is applied, a time-resolved velocity profile can be acquired over the cardiac cycle [17]. Integration of the velocity over the vessel area and over the cardiac cycle represents mean flow. In healthy individuals four distinct features of the flow profile can be described, namely an early rise in flow velocity called the early systolic peak, followed by an incision and a small midsystolic peak as well as a more or less continuous diastolic blood flow [18]. Experimental animal studies have shown that with a continuous increase of the degree of renal artery stenosis a gradual loss of the early systolic peak appears first [19]. Further increase in the morphologic stenosis results in a drop of the midsystolic peak with reduction of mean flow. These characteristic changes in the flow profile in relation to the degree of renal artery stenosis have shown to correlate well with transstenotic pressure gradients [19]. From these results, a clinical useful functional grading scheme can be applied to semi-quantitatively assess the hemodynamic significance of renal artery stenosis by a four scale grading scheme [20]. With further refinements in the acquisition technique using segmented echoplanar imaging an entire time-resolved phase-contrast data set of one renal artery can be acquired within a single breathhold [21]. In combination with breathhold 3D-Gd-MRA, a morphologic and hemodynamic assessment of a renal artery stenosis is possible within a few breathholds [22]. Data from a recent tricenter study has shown the synergistic value of a combined morphologic and functional grading of renal artery stenosis by 3D-Gd-MRA in combination with phase-contrast flow measurements [20]. In comparison with DSA, the number of correctly graded stenoses could be increased from 82 % to 97 % on a 2-point scale.

Other authors have suggested different techniques for assessment of the hemodynamic significance of renal artery stenosis. One of the most intensively evaluated approaches is the use of MR renography applying multiple 3D gradient echo data sets after administration of small amounts of gadolinium chelates in combination with administration of an ACE-inhibitor such as Captopril [23].

## 3. Interobserver variability

A number of publications has recently highlighted the fact that the acceptance of any imaging modality as a standard for the morphologic grading of renal artery stenosis is not only influenced by its accuracy but also by the interobserver variability among different observers [24, 25]. Solely morphology-based imaging modalities such as DSA, MRA or CTA are particularly prone to a high degree of interobserver variability, when only measurements of diameter stenosis are applied. In this respect no substantial differences have been found between 3D-Gd-MRA and DSA [26]. Of interest, the worst interobserver agreement for the assessment of the diameter stenosis occurs for stenoses ranging from 30 to 60 % [16]. New concepts for the grading of renal artery stenosis based on measurements of the cross-sectional vessel area on high resolution 3D data sets have shown to significantly improve the degree of interobserver agreement [16]. This concept can be carried further, if a functional MR modality such as phase-contrast flow measurements is added to 3D-Gd-MRA and both modalities are interpreted together as one comprehensive stenosis grading. This has also shown to significantly improve interobserver agreement compared to both MRA as well as DSA [20].

## 4. Parenchymal versus renovascular disease

As a consequence of a long standing renal artery stenosis, secondary renoparenchymal disease can develop [27]. This ischemic nephropathy is probably an impaired adaptation of the kidney to a more hypoxic state with chronic reduction of blood flow particularly in the medulla [28]. However, more frequently primary parenchymal disease is present unrelated to renal artery stenosis and is the result of common diseases with involvement of the kidneys such as diabetic nephropathy, hypertensive nephrosclerosis or glomerulonephritis. In general, three different methods for MR perfusion imaging of the kidney have been described for renal artery stenosis, namely qualitative assessment of renal perfusion with arterial spin labeling (ASL) techniques without contrast agents, semi-quantitative perfusion measurements with extracellular gadolinium chelates and quantitative assessment of renal perfusion with intravascular contrast agents with absolute parameters of regional renal perfusion [29-32]. A commonly used ASL technique is the so-called flow sensitive alternating inversion recovery method (FAIR) [29]. In one study of 46 patients an overall accuracy of 88% could be achieved to classify kidneys into either healthy or diseased compared to the final clinical diagnosis using a combination of mean arterial blood flow from phase-contrast flow measurements and renal perfusion from arterial spin labeling. One major disadvantage of using arterial spin labeling techniques for renal perfusion imaging is the poor signal to noise of this approach at 1.5 Tesla. This makes the calculation of semi-quantitative or quantitative parameters of renal perfusion difficult and unreliable, although some authors have presented absolute values of renal perfusion with modified ASL techniques and acceptable reproducibility [33]. For absolute quantification of renal perfusion, two different classes of intravascular agents have been used, namely strongly protein binding substances such as MS-325 (Vasovist, Schering AG) or ultra-small particle iron oxides (USPIO) such as

NC100150 (Clariscan, GE Healthcare) [30, 31]. Absolute quantification is essentially performed in 4 steps [31]: first signal changes are transferred into concentration changes assuming a linear relation between R2* and the concentration of the contrast agent. Second, the principles of indicated dilution theory are applied and the regional blood volume is determined from the area under the measured tissue concentration-time curves normalized to the integrated arterial input function. Third, the mean transit time is calculated by deconvolution of the tissue concentration-time curve with the arterial input function to obtain the true residue function within the tissue, i.e. the concentration-time curve in the tissue following an idealized instantaneous arterial input of contrast agent. Dividing regional blood volume by the mean transit time, regional blood flow per gram of tissue can be calculated. In one study, the regional renal blood showed a characteristic variation for the different degrees of renal artery stenosis [34]. While the mean parenchymal blood flow was in the range of 500ml/100g/min for the non-stenosed artery, it significantly dropped to 150ml/100g/min for stenoses exceeding 90 % in the acute animal model. In patients, substantial differences in renal perfusion were found between normal kidneys (approximately 380 ml/100g/min renal regional blood flow) and those kidneys with parenchymal damage exhibiting only a regional renal blood flow of 170ml/100g/min.

A more easy and robust approach for the clinical routine is dynamic MR perfusion measurements with extracellular gadolinium chelates. The recent availability of high performance cardiovascular MRI scanners with improved gradient performance allows the use of saturation recovery gradient-echo sequences that offer high signal linearity and high temporal resolution [32]. The great advantage of this type of functional imaging of the renal parenchyma is that it can be easily integrated into a comprehensive renal exam since only few milliliters of gadolinium chelates are required. In a recent study of 73 patients referred for suspected renal artery stenosis significant differences between patients without or low to intermediate renal artery stenosis and those with high grade stenosis were found for MTT, MUS and TTP [32]. An additional advantage of regional perfusion measurements in the kidneys is the identification of segmental or subsegmental renal artery stenosis. Those perfusion maps have also high potential to identify regional hypoperfusion of the kidney from fibromuscular dysplasia (FMD) induced stenoses of the segmental renal arteries [32]. This distal involvement of the main renal artery as well as affection of intrarenal branches is frequently found in FMD and can usually not be detected by 3D-Gd-MRA due to constraints in spatial resolution, parenchymal overlay as well as random motion in the more distal branches of the renal artery [35].

## 5. Monitoring of renal artery stenosis dilatation during intervention

The necessity for exact mapping of the renal artery stenosis both in terms of true reduction of the lumen as well as its functional significance becomes clear when one looks at the published data for rates of recurrent stenosis as well as cure and improvement rates for both blood pressure and renal function [6, 7, 36]. For all three criteria a large range of published results is found in literature depending on the exact definition of the pre-interventional degree of stenosis. In our institution intravascular ultrasound is used to verify the pre-interventional MRA and intra-procedural DSA mapping of renal artery area The repetitive PTA increased the mean lumen area by 21 % [37].

## 6. Post-interventional therapy monitoring

Phase-contrast flow measurements can be routinely performed distal to the stent deployment

site. In one study, the MR flow curves in the postoperative renal arteries of 12 patients showed a restoration of the normal flow profile with presence of the early systolic peak, the early systolic incision, the midsystolic peak and the diastolic blood flow [18]. The three blood flow parameters mean blood flow, maximum velocity and time to maximum velocity demonstrated significant changes in comparison to the preoperative data.

## 7. Prediction of improvement after interventional therapy

The publication in the New England Journal of Medicine by Radermacher J et al. has advocated the importance of ultrasound resistance index measurements for predicting the therapeutic benefit in patients with RAS and impaired renal function in terms of an improved creatinine clearance [38]. This study found a resistance index </> 0.8 to be a potent discriminator between those two patient groups. Currently, no other imaging modality has been able to demonstrate its value in order to predict an improvement of renal function after interventional therapy. An ongoing trial, the PROFIT (prediction of renal outcome following interventional therapy) study is designed to compare the functional MRI parameters including flow and perfusion versus the currently established ultrasound resistive index [39]. One of the remaining problems is that pharmacologic stressing of the kidney has not yet been demonstrated with imaging modalities. This might be one key step to resolve the problem if persistent vasoconstriction is present in the small intrarenal arteries that may restrict functional improvement after revascularisation. In this respect, intrarenal oxygenation measurements by means of R2* mapping with multi-echo gradient-echo sequences appear to be of high potential [40]. Results from volunteer studies and patients with diabetes have already shown that the decrease of prostaglandine E synthesis leads to a reduction of blood flow particularly in the medulla and consequently to a significantly diminished response of renal blood flow to an oral water load [41, 42].

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